REMARKS

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections in view of the foregoing amendments and following remarks.

Applicants wish to make co-pending application, U.S. Serial No. 10/517,518 of record in this application. The application discloses guanidino phenylalanine compounds and liposomal formulations; however there is no disclosure of encapsulating the compounds within a liposome.

Claim 57 is a new dependent claim wherein the formulation reduces unwanted side effects such as hemolysis or skin irritation. Support for this claim is found on page 4, lines 32-33; page 21, lines 27-32; Fig. 2; Table 3; and Example 5.

Claim Rejections- 35 U.S.C. § 103

Claims 28-37, 41-48 and 53-56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00 04954 for teaching the claimed compounds and further suggesting their incorporation into liposomal membranes. Additionally, the Examiner cites the references of Leigh, 6,599,527; Janjic, 6,168,778; Weiner, 5,049,392; and Yau-Young, 5,023,087 for encapsulating active agents in a liposome.

Claims 28 and 48 have been amended to place the claims in better condition for examination. Claim 28 has been amended to limit the formulation to comprise a 3-guanidino phenylalanine derivative or consist essentially of a 3-amidino derivative, both having reduced side effects. WO 00 teaches inhibitors derived from 3-amidinophenylalanine. Claim 28 restricts its formulation to consist essentially of a 3-amidinophenylalanine derivative with the limitation that the formulation results in the reduction of unwanted side effects. Applicants believe claim 28 is thus allowable over the prior art. Claim 48 was a previous claim which has been amended to claim a formulation for intramuscular injection.

In response to the rejection of claims 29-37, 41-48 and 53-56, given that claim 28 is allowable over the cited art, it follows that claims 29-37, 41-48 and 53-56, all depending on claim 28, should also be allowable.

The Examiner cites Ben-Hur, 6,010,890, and Kurono, 4,906,477, as teaching that liposomes reduce the hemolysis of active agents. The Applicants respectfully disagree. Upon reading the Ben-Hur, and Kurono references, one of skill in the art would not predict that the use of a liposome would necessarily prevent side effects. Ben-Hur is concerned with a photosensitizer, silicone phthalocyanine (Pc4), in a liposomal carrier. The type of composition and the respective activity is different from the amidino and guanidino compounds of the present invention.

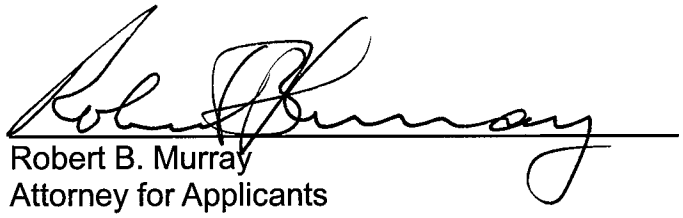
Ben-Hur reports in col. 6, lines 62-65 that "...formulation of Pc4 in liposomes resulted in less hemolysis ...", however, it is stated in col. 7, lines 15-19 and Fig. 4, that "The results (Fig. 4) show great differences in the ability of equivirucidal doses to cause red blood cell damage, depending on the liposome composition." Col. 7, lines 1-4 further state that "Compositions containing PEG or cholesterol... also reflected in greatly enhanced hemolysis of red cells." Thus, contrary to the Examiner's assertion, Ben-Hur does not teach that liposomes reduce hemolysis of active agents.

Regarding the Kurono reference, Kurono did not test his liposomal mixture with a high concentration of adriamycin. The highest concentration of adriamycin used with liposomes was 176μM, and the result was non- detectable hemolysis. There is no direct comparison of free vs. liposomal adriamycin at the same concentration, but the nearest concentrations of free adriamycin were 125μM, and 250μM which caused 0.7% and 8.8% hemolysis, respectively (Table 1). According to Kurono, the free adriamycin only "exhibited slight hemolytic activity," (col. 7, lines 9-10). The 176μM used in the liposome falls in the low end of the range of free adriamycin tested. If one had to predict, this concentration may have produced a few percentage points of hemolysis, which does not appear statistically significant, and would depend on the slope of the curve of the dose-response between 125μM and 250μM, which is unknown. The expected hemolysis for 176μM may be 1% or 4%, which is still not significant. The liposome thus prevented a less- than slight hemolytic effect.

Moreover, Kurono's hemolytic activity was tested *in vitro*, which does not guarantee *in vivo* results. Also, Kurono relates to an encapsulated adriamycin which is a member of the group of anthracycline antibiotics, which differ from the amidino and guanidino compounds of this invention. The target organs are also different, as the aim of Kurono is to suppress the side effects of cardiotoxicity and nephrotoxicity (col. 2, lines 23-25). There is no teaching on skin irritation.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections. Early and favorable action is awaited.

Respectfully submitted,

By 

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